

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

METOLACHLOR

Chemical Code #: 001996; Tolerance # 368
SB # 087

Revised: 10/7/86, 4/7/88, 11/20/89, 12/10/90, 8/29/97

I. DATA GAP STATUS

Combined (chronic & onco), rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T970829

Revised by M. Silva, 11/89; 12/90; P. Leung, 8/29/97

Rectified through volume 298; record #: 138560

Additional information on Metolachlor: Guidance for the Reregistration of Pesticide Products Containing the Active Ingredient Metolachlor (108801); Case Number 0001; CAS 51218-45-2. USEPA, Office of Pesticide Programs, Washington, DC, 1/87.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

Subchronic Studies

209 (no record #) "Four-Week Pilot Study With Albino Rats," (IBT, 11/13/75). Metolachlor (purity unknown) was fed to "albino rats" (5/sex/group) at 0, 300, 1000, 10000, or 30000 ppm for 28 days. Diets were prepared fresh daily. Information presented for this study was two tables showing body weight and food consumption for the 28 days. At \geq 3000 ppm both food consumption and body weights decreased, however, it appeared 3,000 ppm was well tolerated. This test served as the basis for choice of dose range for the definitive study (035280), which was 0, 300, 1000 and 3000 ppm. No other data were provided. **These data are supplementary.** M. Silva, 10/6/89.

053 988462 "Three-Month Oral Toxicity Trial," (The Ongoing Research and Breeding Center, 3/1/74). Metolachlor Technical (93.8% pure, batch #: CGA 24 705) was fed, in diet for 13 weeks to Sprague-Dawley (A) rats at 0 (vehicle = alcohol; 30/sex) or Group I - 100 ppm (20/sex) from week 0 to 10 and 2000 ppm from week 10 to 13 (10/sex). Group II - 300 ppm (20/sex) for 13 weeks and Group III - 1000 ppm from week 0 to 13 (20/sex) and using additional animals, 1000 ppm from week 0 to 10 (10/sex) and 2000 ppm from week 10 to 13. At the end of week 13, controls (10/sex) and 2000 ppm (10/sex) animals were kept for recovery, then sacrificed at week 17. NOEL = 2000 ppm (no effects observed at any dose level). **No adverse effect.** This study is supplementary to 035280. M. Silva, 10/11/89.

Combined Studies

**** 144-150, 209 035280-035286** "Two Year Chronic Toxicity and Oncogenicity Study With Metolachlor in Albino Rats," (Hazleton Raltech, Inc., 5/2/83). Metolachlor technical (95.4%) tested in the diet at 0, 30, 300 and 3000 ppm for 24 months; 60/sex/group; 10/sex/group at 0, and 3000 ppm for recovery study at 12-13 months. Systemic NOEL = 300 ppm (decrease in body weight in females at 3000 ppm; increased liver and testes weight in males and cholesterol (both sexes) at 3000 ppm. **Possible adverse effect.** Oncogenic NOEL = 300 ppm (increase in eosinophilic foci of hepatocellular alteration (both sexes) at 3000 ppm; increase in neoplastic liver nodules in males and females at 3000 ppm--24 months--statistically significant in females). This study was initially reviewed as unacceptable (Apostolou, 9/26/85 and Choy, 10/20/86) as a combined study but acceptable as an oncogenicity study only (M. Silva, 3/21/88). Upon submission of new information (368-209) and rebuttal discussion of 2/21/89 regarding the necessity of an ophthalmological exam, the study is now complete and **acceptable** as a combined (chronic & oncogenicity) study. M. Silva, 10/30/89.

EPA One-liner: Core Minimum; onco NOEL not stated, systemic NOEL = 300 ppm

210 071537 "Two-Year Chronic Oral Toxicity Study With CGA-24705 Technical in Albino Rats," (IBT, 2/9/79--EPA Supplemental). Metolachlor technical (Batch #: FL-750227; 99.9% and FL-752105; 96.5%) was fed in diet to Charles River CD rats at 0, 30, 300, 1000 and 3000 ppm for 24 months. **Possible adverse effect.** NOEL = 1000 ppm (decreased body weight, increased incidence of hepatocellular hypertrophy in males, hepatocellular carcinoma and cystic cholangioma in females). This study is supplementary to 035280. M. Silva, 11/7/89.
EPA One-liner: Core Grade Supplementary

CHRONIC TOXICITY, DOG

Subchronic Study

060 988465 "Three-Month Oral Toxicity Test of CGA 24 705 in Dog," (The Oncins Research and Breeding Center, 3/1/74). Metolachlor technical (93.8% pure) was fed in diet for 15 weeks (plus a 4-week reversibility trial) to beagle dogs (4/sex/group) at 0 (vehicle = water), 50 (from week 1 to 9), 150, 500 and 1000 (from week 9 to 15). Dogs from the 0 and 1000 ppm groups were used for the reversibility trial. **No adverse effect indicated.** NOEL \geq 1000 ppm (no significant effects were observed at any dose level). This study is supplementary to 044404 and 071538. M. Silva, 11/2/89.

Chronic Studies

** 211, 298; 071538, 138560; "Chronic Toxicity Study in Dogs," (Hazelette, J.R., CIBA-GEIGY Corporation, Division of Toxicology/Pathology and Met Path Laboratories, Laboratory Study Number 862253, 1/23/89). Metolachlor technical (97% purity, Lot #: FL861768) was administered in feed at concentrations of 0 (vehicle = acetone), 100, 300 or 1000 ppm to Beagle dogs (4/sex/group). In addition, after 52 weeks of treatment, a 4 week recovery group (2/sex/group) was included. NOEL = 300 ppm (Significant increases were observed in mean alkaline phosphatase levels in females at 1000 ppm. Significant decreases in bodyweight gain and food consumption was observed in both sexes at 1000 ppm.) NOAEL = 1000 ppm (No significant effects were observed at any dose level.) **No adverse effect indicated. Acceptable.** (Kishiyama & Silva, 12/4/90).

161 044404 (with rebuttal and additional information in -196 055162): "Six-Month Chronic Oral Toxicity Study in Beagle Dogs," IRDC, 5/21/80. Metolachlor technical, 96.3% pure, in the feed at 1000, 300, 100, or 0 ppm to 6-8/sex/level for 6 months, with 4 week recovery of 2/sex at 1000 or 0 ppm. **NO ADVERSE EFFECT**, slight serum alkaline phosphatase and liver weight changes, NOEL=300 ppm; Unacceptable but upgradable only as subchronic in prior review (Choy, 10/10/86); **UNACCEPTABLE** and not upgradable for chronic data requirement in second review - no MTD or target organ toxicity. F. Martz, 1/7/88.

EPA One-liner: NOEL = 100 ppm, LEL = 300 ppm (clinical chemistry and hematology changes; increased weight of thyroid gland in females). Core Minimum. EPA states that an MTD is not required in a dog study.

ONCOGENICITY, RAT

See combined, rat (above)

ONCOGENICITY, MOUSE

Subchronic Study

209 (no record #) "28-Day Mouse Pilot Study With CGA-24705 (IBT #: 622-07857)," (IBT, 1975). Metolachlor (purity & grade unspecified) was fed to albino mice (unspecified strain) in diet for 28 days (5/sex/group) at 0 (vehicle unspecified), 100, 300, 1000, 3000, 10000, 30000 or 100000 ppm. All animals treated at 100000 ppm died in the first week of treatment, however no

animals treated at lower doses experienced mortalities. Growth and food consumption was normal in animals treated at ≤ 3000 ppm. Body weight loss was observed in animals fed ≥ 10000 ppm. It was suggested to Ciba-Geigy by IBT that dietary levels for the chronic mouse study (oncogenicity study 988476-78) be 0, 300, 1000 and 3000 ppm. These data are supplementary and consist of summary data only. M. Silva, 11/1/89.

Oncogenicity Studies

** 151-154, 209 035287-90 "Carcinogenicity Study With Metolachlor in Albino Mice," (Hazleton Raltech, Inc., 8/31/82). Metolachlor technical (purity = 96.4%) was tested in diet at 0, 300, 1000 and 3000 ppm for 24 months (52/sex/group) with an additional 16/sex/group for samples at 8, 12 and 18 months. **No adverse effect.** NOEL = 1000 ppm (decrease in body weight, both sexes; increase in AST, ALT and alkaline phosphatase in males and increase in urine protein; decrease in spleen and seminal vesicle weight in males and uterus weight in females; possible increase in nodular hyperplasia in liver in males). There was no dose-related increase in neoplasms. Previously reviewed as unacceptable (Apostolou, 9/27/85 and Choy, 10/21/86), upon submission of the requested information (justification of dose selection), the study is now **acceptable**. M. Silva, 11/2/89.

EPA One-liner: Core Minimum.

054-055, 988476, 988478 "Carcinogenicity Study with CGA-24705 Technical (Metolachlor) in Albino Mice, Final Report." (IBT, 12/15/77) Metolachlor (99.9 and 96.5%) given in the diet at 0, 30, 1000 or 3000 ppm for 18 months (males) or 20 months (females); 50/sex/group; no consistent toxicological effects noted, MTD may not have been achieved; onco NOEL > 3000 ppm; **unacceptable**; not upgradeable (no analysis of dosing material, no justification of dosing levels, food consumption not measured, body weights not recorded for first 4 months, no hematology data, incomplete histopathology). Gee, 4-22-85.

EPA One-liner: onco NOEL > 3000 ppm; Core Minimum.

REPRODUCTION, RAT

** 163-165, 209 044406-044408 "Two Generation Reproduction Study in Albino Rats With Metolachlor Technical," (ToxiGenics, 8/31/81). Metolachlor technical (95.4% pure) was tested in diet at 0, 30, 300 and 1000 ppm in a two generation, one litter/generation study (15 males/group & 30 females/group). **No adverse effect.** Reproductive NOEL = 300 ppm (decrease in food consumption in F1 females; decrease in F1 & F2 progeny body weights). Previously reviewed as unacceptable (Choy, 10/7/86) because dose level was not justified and it was believed that a MTD had not been reached, upon submission of requested information, the study has been upgraded to **acceptable**. M. Silva, 10/31/89.

EPA one-liner: Reproductive NOEL = 300 ppm (reduced pup weights in the F1a and F2a litters). LEL = 1000 ppm; Core Guideline.

049, 988486 "Three-Generation Reproduction Study with CGA-24705 Technical (Metolachlor) in Albino Rats, Final Report." (IBT, 12/15/77) Metolachlor (96.5%) tested in the diet for a 3-generation, 2 litters/generation study at 0, 30, 300 or 1000 ppm; 8 males/group, 16 females/group; reduced mating index at all dose levels; **unacceptable**; not upgradeable

(inadequate number of animals per group; no justification of dose levels, dosing schedule differs from guidelines, inadequate histopathology, disease and mortality problems). Gee, 4-22-85.

EPA one-liner: NOEL=300 ppm; LEL=1000 ppm; Supplementary.

Note: The IBT study indicated that there is a possible adverse effect but a more recent and complete ToxiGenics study did not indicate an adverse effect. We therefore conclude at this time that there is no adverse effect in the reproduction study. Choy, 10/86.

TERATOLOGY, RAT

050, 988480, 988481 "Reproduction Study CGA-24705 Technical (Metolachlor), Rat Segment II (Test for Teratogenic or Embryotoxic Effects)." (Ciba-Geigy, 6/21/76) Metolachlor (purity unspecified) given by gavage at 0, 60, 180 or 360 mg/kg/day on days 6-15 of gestation; 25/group; maternal toxicity not noted at high dose; maternal, teratogenic and fetotoxic NOELs>360 mg/kg; **unacceptable**; possibly upgradeable with justification of dosing levels, purity of test article, analysis of dosing solution, fetuses not sexed, corpora lutea not counted. Gee, 4-19-85.

EPA one-liner: maternal teratogenic and fetotoxic NOELs>360 mg/kg; minimum.

** 162 044405 "Embryo/Fetal Toxicity and Teratogenic Potential Study of CGA-24705 (FL-841697) (Metolachlor) Administered Orally via Gavage to CRL:COBS CD (SD)br Presumed Pregnant Rats, Final Report." (Argus, 8/6/85) Metolachlor (96.4%) given by gavage at 0, 30, 100, 300 and 1000 mg/kg/day on 6-15 days of gestation; 20 to 24 pregnant animals/group; maternal toxicity noted at 1000 mg/kg/day (animal death and adverse clinical signs); maternal NOEL=300 mg/kg/day; developmental NOEL=300 mg/kg/day; no adverse effect; **acceptable**. Choy, 10-1-86.

TERATOLOGY, RABBIT

155 035291 "Teratogenic Potential of CGA-24705 (Metolachlor) in New Zealand White Rabbits (Segment II Evaluation)." (Argus, 7/25/80) Metolachlor (95.4%) given by gavage at 0, 36, 120 or 360 mg/kg/day on days 6-18 of gestation. Maternal NOEL = 36 mg/kg (decreased food consumption, miosis and decreased body weight gain at 120 and 360 mg/kg; blood in cage pan at 360 mg/kg). Developmental NOEL = 360 mg/kg (no consistent fetotoxic or teratogenic effect noted). This study was originally reviewed as unacceptable (analysis of dosing solution, pup brains not examined--Apostolou, 3/30/85). Upon receipt and evaluation of information requested by CDFA (196 055161), this study is now **acceptable. F. Martz and M. Silva, 3/15/88.

EPA one-liner: maternal NOEL=120 mg/kg, fetotoxic and teratogenic NOEL>360 mg/kg; minimum.

GENE MUTATION

051 988487 "Salmonella/Mammalian-Microsome Mutagenicity Test with CGA 24705 (Test for Mutagenic Properties in Bacteria) (Technical Metolachlor)." (Ciba-Geigy, 8/30/76) Metolachlor (purity unspecified); tested at 0, 10, 100, 1000 or 10,000 ug/0.1 ml on Salmonella

strains TA 98, 100, 1537 and 1538 with S9; no indication of increased mutation frequency; **unacceptable**; possibly upgradeable (data on positive controls not included, test article purity not indicated, incubation time not indicated, inadequate description of preparation of the S9). Gee, 4-19-85.

** 166, 044413 "L5178Y/TK+/- Mouse Lymphoma Mutagenicity Test, CGA 23705 (Metolachlor) Technical, Final Report." (Ciba-Geigy, 12/5/84) Metolachlor (95.5%) tested at 10.5 to 280 nl/ml with S9 activation and 9.5 to 190 nl/ml without S9 activation on mouse lymphoma cells L5178Y/TK^{+/-}; 4 hours exposure. **No adverse effect**. Initially reviewed as unacceptable (W. Choy, 9/25/86) based on a single trial without S9 activation. Upon reconsideration, the study is upgraded to **acceptable**, based upon the repeat trial with activation. Gee, 4/6/88.

CHROMOSOME

050, 988488 "Dominant Lethal Study on CGA 24705 Technical Mouse (Test for Cytotoxic/Mutagenic Effects on Male Germinal Cells) Also Addendum Included (Metolachlor)." Ciba-Geigy 9/8/76) Metolachlor (purity unspecified); tested at 0, 100 and 300 mg/kg on albino NMR1-derived mice in dominant-lethal assay; single dose by oral gavage; 20 males/group; 1 male/2 females for 1 week with 6 pairing periods; no evidence of adverse effect; **unacceptable**; not upgradeable (no evidence of toxicity at highest dose, purity of test article, analysis of dosing solution, no positive controls, only two dose levels, frequency of weighings and observations not clear, body weight data missing). Gee, 4-19-85.

EPA one-liner: non mutagen; Core minimum.

166, 209 044409 "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster, Final Report," (Ciba-Geigy, 10/26/84). Metolachlor technical (95.9% pure) was administered orally by gavage at 0, 1250, 2500 and 5000 mg/kg (limit test) on two consecutive days to Chinese hamsters (3/sex/group) for micronucleus and polyploidy induction assays (1000 bone marrow cells/animal scored). Sampling time was 24 hours after the last dosing. **No adverse effect. Previously reviewed as unacceptable (Choy, 9/26/86; Gee, 4/6/88--no justification for sampling time or for number of animals used), upon receipt of the requested information, the study has been upgraded to **acceptable**. M. Silva, 11/8/89.

DNA DAMAGE

166 044411 "Autoradiographic DNA Repair Test on Human Fibroblasts, CGA 241705 (Metolachlor) Technical." (Ciba-Geigy, 11/20/86) Metolachlor (95.9%) tested in in vitro UDS assay at 0, 0.125, 0.625, 3.125 and 15.625 nl/ml on human fibroblasts; 5 hours exposure without S9 activation; no adverse effect; **unacceptable**; not upgradeable (insufficient cytotoxicity, no activated trial). Choy, 9-26-86.

** 166 044412 "Autoradiographic DNA Repair Test on Rat Hepatocytes, CGA 24 705 (Metolachlor) Technical." (Ciba-Geigy, 11/20/86) Metolachlor (95.9%) tested in in vitro UDS assay at 0, 0.25, 1.25, 6.25 and 31.25 nl/ml on rat hepatocytes; 5 hours exposure; no adverse effect; **acceptable**. Choy, 9-26-86.

Supplementary Studies

368-282, 298; 138125, 138558; "21- Day Dermal Toxicity Study in Rabbits" (F. Mastrocco, et. al., Pharmaceutical Div., Ciba-Geigy Corp., Summit, NJ, Report # 86141, 11/16/87). Metolachlor Technical (FL 841697, batch P.304015, 96.4% purity) was administered dermally to intact skin of rabbits at daily doses of 0, 10, 100, or 1000 mg/kg for 6 hours/day for 21 consecutive days. 5 New Zealand white rabbits/sex/dose were used. All animals survived the study without any treatment-related clinical signs or changes in body weight. Erythema (grade 1 or 2) and dry skin at application site were reported in all treated animals as early as days 4 and 6, respectively, and throughout the study. Fissuring of the skin was observed in 1/5 low dose and 2/5 mid dose females on days 11 and 12. Also, fissuring was noted in 2/5 mid dose males between days 8 and 18 and in all high dose animals between days 6 and 21. Necropsy revealed increased relative liver weights in high dose males and relative kidney weights in high dose females. Histopathology indicated increased incidence of hyperkeratosis in all treated males and in mid and high dose females. NOAEL(M/F) = 1000 mg/kg/day **[No adverse effects]**. Dermal NOEL (M/F) < 10 mg/kg/day (dermal effects); Systemic NOEL (M/F) = 100 mg/kg/day (increased relative liver and kidney weights). **Acceptable** (Leung, 8/29/97).